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SUMMATION

Roger W. Sperry

SPERRY: I would first like to add a couple of points, quickly, related to the growth problem. The first concerns the specificity of nerve growth, which hasn't been mentioned: The evidence from a variety of development and regeneration studies (44) leads us to believe that the nerve cells are really a diverse population of individuals distinguishable one from another in their chemical features. This chemical specificity, we believe, determines which other cells each neuron will hook up with, and is a critical regulating factor in the ontogenetic patterning of the central pathways and connections. This means that there must be literally millions of chemically distinguishable neurons on either side of the midplane, with a corresponding population of mirror twins across town on the opposite side.

In experiments on nerve growth, we are repeatedly impressed, as anyone is apt to be who works in experimental embryology, or with microanatomy, or pharmacology, or pathology, rather more than the electrophysiologist, perhaps, with the tremendous diversity in the properties of neurons, their differential growth and regenerative capacities, their different morphologies, migratory and pulsatory tendencies, staining capacities, their reactions to drugs, infectious toxins, and so on, down the line.

I won't go through the evidence, which is a long story and has been reviewed elsewhere. The data suggest simply that cells do connect up selectively with the particular neurons they are supposed to connect with. Not only do they selectively attach to the proper target cells, but they also find their way to their terminal areas in the CNS, on a very selective chemotactic kind of homing behavior. Most of the experiments involve the cutting of fiber bundles that are functionally heterogeneous, and scrambling them, after which the various fiber types unscramble themselves and regain their proper synaptic associations to restore orderly function.

It is not impossible that these developmental specificities that govern the patterning of the central nerve networks in development,

may be involved also in any alterations produced in the networks by experience. This brings me to the second point I wanted to make. It deals with the end-organ induction of specificity in some of the peripheral neurons and its effect on selective central synapses. In some ways, this is a memory-like effect within nerve cells that determines their functional connections with other nerve cells. Take, for example, a cutaneous neuron of a lumbar spinal ganglion. The fiber grows out and, as a result of its contact or experience with a particular type of skin or other end-organ, it hooks up centrally in a particular way, for the rest of its life, forming synaptic connections appropriate to the particular point in the skin or the point in the periosteum or vestibular system, muscles, and so on.

Let's say the nerve fiber grows out and comes in contact with the tip of the big toe instead of with the side, or with the inside of the toe instead of the outside. As a result of this peripheral exposure, it takes on the specificity of the given cutaneous area. Something is then transmitted centrally along the fibers, probably to the cell nucleus, and the whole cell stretching up to the base of the neck then becomes differentiated from neighboring cells that happened to contact a few millimeters over at other areas in the skin. As a result, the central synaptic terminals of this fiber at all levels of the cord, thousands of them, all connect differently in a systematic way from the fibers right beside them in the same neuropile, the peripheral ends of which happened to connect with the toe nail or with any other remote cutaneous area.

The effect, as I say, persists for the rest of the animal's life, unless the peripheral fiber is severed and grows back to a new cutaneous region. If this should occur before developmental plasticity is lost, the specificity may change and the functional relations in the centers may alter accordingly. There are many parallels here with the immunity effect, also, and the possibility of common cellular mechanisms in memory, end-organ induction, and immunity is evident. Morphogenetic gradients are directly implicated, but the phenomenon requires more than just a concentration gradient: The specification of the neuron must involve something that is replicable and can be distributed throughout the arboritic ramifications of each fiber, up and down the cord into these thousands of fine terminals, without being disturbed. Each terminal of each of the thousands of cutaneous fibers, to stay with our initial example, has to maintain its specific chemical property.

The rest of what I have to say as "summarizer" aims more at trying to relate to the memory problem as a whole some of the material that Sir John and Dr. Kruger presented.

I made brief reference to what might be called the problem of how instinctive memory gets organized and built into the brain. I indi-

cated that the inherent patterning of the brain pathways and the synaptic connections, even in refined detail, is all predetermined by growth mechanisms, with special reference to chemical differentiation of the neuron population. Developmental forces of this sort take care of the patterning of the synaptic associations, insofar as these synapses are built-in rather than learned. As far as I know, among all the synapses that have been observed in the history of neurology, not one of them has yet been demonstrated to have been implanted by learning. In other words, the great bulk of the synaptic contacts, certainly below the cerebral cortex, are built-in, not acquired through experience.

All this evidence applies to the developmental patterning of the brain network, that is, to the organization of the morphology of the circuitry.

There is, however, another kind of factor, that I assume to be extremely important, about which we have no evidence as yet, but which is probably worth mentioning. This basic differentiation of the neuron population presumably has important effects also in regard to the development of the intrinsic physiologic properties of the neurons, as well as to the contacts they form with each other. I am thinking of such things as whether the neurons are going to be excitatory or inhibitory, whether they will use this or that transmitter, whether their resting baseline threshold is going to be low or high, whether they will discharge spontaneously or only upon stimulation, whether they will discharge rhythmically or arhythmically, whether they tend to discharge at one particular frequency or another, whether they tend to fire in bursts or in trains, and whether the bursts are short or long, and so on.

In the context of our coming discussions, I did not want to leave the impression that it is only the networks and the contact relations that are critical in phylogenetic memories. It is very possible, and even probable, that these other factors relating to the intrinsic physiologic properties are also extremely important. So far, however, we just don't have any experimental evidence on these intrinsic factors.

Many of these embryonic differentiation concepts apply, of course, to the glial systems and to other neighboring elements in lesser degree, regardless of what the functional role of the glia may yet prove to be.

It might be well to pause here for any questions along this line, since I am going to turn now to quite different matters.

MILLER: Do you have any evidence that this is a chemical code or is it just that a chemical code is the only kind you can imagine that would work?

SPERRY: I think the latter. Just as Sir John has referred back to a long history of neurophysiology, behind some of his remarks, so too one can point to a mass of background material in the history of embryology that makes the chemical code seem a very reasonable supposition.

ECCLES: I am very attracted by this suggestion of yours. Recently, for example, in a good many sites I mentioned earlier, we have found that inhibitory synapses are restricted to the perikaryon, to the area around the nucleus, and that the excitatory ones are out on the dendrite, largely on the spines.

When we consider how this gets put together, we can watch, as far as we know, the neuroembryological story, and it looks as if the terminal branches from the inhibitory cells, which, of course, are chemically specified, are smelling out, or chemically sensing, if you like, certain areas which they find much more attractive than others. We propose the simple idea that the perikaryon area will smell differently to these inhibitory terminals. This area is, after all, the part closest to the nucleus; so presumably it can be metabolically distinguished from more remote parts of the cell; and this might be, in fact, the determining influence on the strategic siting of inhibitory synapses on the perikaryon, near to the axon, and the more remote siting of the excitatory synapses. The excitatory synapses don't like the smell of the perikaryon and, therefore, have to be stuck out on dendrites and even on spines, that are still more remote.

ROBERTS: When are these connections formed? Are they formed when the dendritic arborization is already extensive, or are they formed when there are relatively few dendrites, so that the probability of hitting the perikaryon is greater than that of hitting the dendrites?

ECCLES: I think I can answer that. The excitatory synapses are formed at least as soon as the inhibitory ones, and yet they go to the dendrites while the inhibitory synapses go to the soma. In fact, if you study the embryological development of the synaptic excitatory and inhibitory synaptic connections in the cerebellum, they show that there is an actual transfer. Initially, some excitatory synapses are on the soma and then move as climbing fibers up the dendrites, and the inhibitory synapses growing from the basket cells come in and occupy the somatic sites.

PRIBRAM: Some of your work on the red muscle and white muscle might be mentioned here.

ECCLES: Yes. Nerve cells in the spinal cord are of two types: the tonic and the phasic. The tonic ones have a rather long after hyperpolarization with slow frequency of firing, and they can specify the muscles that they grow to, to make them appropriately slow in contraction time. We now know that this is largely due to a change in muscle active state, which is the essential active process responsible for the muscle contraction.

SPERRY: Yes, there are quite a few embryologic phenomena of this sort, that is, the induction of end-organ differentiation by growing nerves at their tips, and the effect may be selective accord-

ing to the type of nerve. In other cases, the end-organ tissue determines the direction of differentiation. Actually, both factors are usually involved to varying degrees depending on the exact conditions.

UTTLEY: You said no synapse was implanted by learning, as far as you know. Would you agree that there may be evidence that synapses will degenerate from lack of learning? —which is rather close to the other statement.

SPERRY: I don't recall any conclusive evidence for this. There seems to be good evidence that synapses, and even whole neurons, will regress from lack of use, but to say that it is a lack of learning is something else. Lack of use may be involved here but isn't it often more than just a lack of use? It involves trophic disturbances of a kind that occur even antidromically and without changes in the excitatory load as in denervated sense organs.

RIOCH: Is there also, in the muscle, the multineuronal innervation seen in the embryo?

ECCLES: I don't think so.

RIOCH: No? It used to be in the literature a long time ago.

ECCLES: There are, of course, polyneuronal innervations of muscle fibers when they are long enough, even in the adult, but I don't think now that there is any belief in multiple innervation that is then regressive in development. Perhaps, somebody could correct me on this.

SPERRY: There are, in the development of the nervous system, examples where there is an initial excess of neurons and, in a way, also an excessive innervation that later regresses (11, 22). But I wouldn't say it is a regression from lack of use or, certainly, not from lack of learning or memory in the embryo.

KRAMER: In the case of the red and white muscle, is the activity correlated with myoglobin content?

ECCLES: Yes.

KRAMER: In other words, you are suggesting that the phasic and the tonic nerves are determinants of the myoglobin content of the muscle and related enzymatic substances?

ECCLES: Yes. Of course I should add that the myoglobin content was observed only roughly by visual observation, and, in fact, it was the color change that put me onto the story of change in muscle speed after nerve cross-unions. Nobody has, in effect, quantitatively evaluated this, but I think that Ernst Guttmann in Prague is now going to do so.

KRAMER: There is a similar story in the flight muscles of cockroaches, except that, in this case, the respiratory pigment is cytochrome c, not myoglobin.

TEUBER: Sir John, the question would be, which way the specification works, whether inward from the muscle to the spinal moto-

neurons or outward via the motoneuron to the muscle. According to Barron's earlier reports (6), it looks very much like a specification that moves inward, doesn't it, Dr. Sperry?

SPERRY: There are so many variations on these different sorts of phenomena to be seen in different parts of the musculature and in different species that one can get answers both ways, and find examples of either.

TEUBER: But, in terms of finding a possible model for some of those changes that occur much later—

KRAMER: There are such models in experiments with insects. The point you raise is exemplified in the pink flight muscles of adult cockroaches. In the nymphal stage these same muscles are white, and it is at, or just subsequent to, metamorphosis that they begin to change into pink muscles. As far as I know, the innervation to these muscles does not change. These insects are capable of continuous use and activity of these muscles just prior to, during, and after metamorphosis. Williams and Schneiderman (49), and others before them, have shown that the nerves are necessary for the development of adult muscles from the pupal muscle anlage in the metamorphosis of Lepidoptea. In the case of cockroaches, however, the nerves may be necessary, but they do not appear to be the only factor required for the increase of the respiratory pigment, cytochrome c, of the flight muscles.

PRIBRAM: Some of Sir John's experiments, however, make it quite clear that induction can proceed from the nerve to the muscle. I was very surprised at this result when I first heard of it, but the experimental evidence appears to be conclusive.

ECCLES: Dr. Sperry and Paul Weiss were in this long before I was, and I'm only following on with their concepts in this respect, as well as those of J. Z. Young. There is the principle of double dependence, muscle on nerve and nerve on muscle, as Young calls it.

SPERRY: There tends to be, pretty much in general, a trophic interdependence among all elements of the sensory-neuro-motor system.

ECCLES: Yes.

PRIBRAM: I think that is an overly condensed statement. Perhaps we should say that, in some instances, it is the muscle that specifies its nerve, but, in other instances, it is nerve that specifies its muscle. It isn't just that these two determine each other, reciprocally.

ECCLES: And, of course, the specification operates for quite different properties, that are quite sharp and specific.

ROBERTS: Dr. Kramer, was the cytochrome c formation during metamorphosis dependent on hormonal changes? Is that your idea?

KRAMER: Well, you're anticipating a problem that I intend to begin working with — the problem of hormonal involvement in this entire mechanism. There is some evidence of hormonal involvement in

the development of the length of the wings of orthopteran insects. The size of the wings in different species, and even within species where both brachypterous and macropterous forms are found, appears to be dependent upon hormonal factors. In all the cockroach species that I have looked at, the absence of visible pigment in the flight muscles is correlated with reduced wings, so I would suspect that the hormonal mechanism responsible for the length of the wings might also play a role in the development of the pink muscle.

ROBERTS: So the hormonal mechanism could unveil some previously inhibited genetic potentiality?

KRAMER: Yes. Certainly the muscle has the capacity to change. It actually does change from a white to a pink muscle in those species in which the adults have pink flight muscles -- so the capacity is there for either state. In the case of Periplaneta americana, where the male adult has pink flight muscles and the female adult has corresponding white muscles, the female simply retains the nymphal form of the musculature. The male goes on to develop a pink-colored, higher cytochrome c content musculature after metamorphosis, together with other differences such as succinoxidase activity, ATPase activity, diphosphopyridine nucleotide, and diphosphothiamine (7).

SPERRY: I think I mentioned that my aim is not so much to try to condense or reiterate the things that we have been over, as to try to put some of the phenomena that Sir John and Dr. Kruger were discussing earlier into the more general setting of the memory problem, that is, of learning and forgetting, as a whole.

I have a series of points to make. First, I would think it certainly very reasonable and possible that the synaptic potentiation and/or the growth phenomena that Dr. Kruger hopefully thinks are there, could be the answer to the biological basis of memory. Synaptic and growth changes such as these could well be the primary changes constituting the so-called engram or permanent memory trace. At the same time, I believe we want to recognize that there have been objections to these and to similar suggestions in the past, which I suspect the learning theorists will remember and some of which I may be able to recall. An example is the law of the effect which says there must be something more than just the use of synapses; there must be, in addition, some kind of retroactive feedback for reinforcement of good effects versus bad effects in terms of the going concern, tension, or goal of the organism at the time. Responses that have a good effect tend to be retained, repeated, and remembered, while those that do not fit in are abondoned, lost, and forgotten.

Also, there is the old objection that a growth process is too slow for a lot of learning. Now that we commonly accept a dual, or more multiple, approach to memory, with a short-term type that carries over for 30 to 45 minutes, I suppose one might say that very small

growth effects, such as those involved in the enlargement or addition of a new synapse, might well be achieved in such a time period.

The general idea—and this was mentioned, I think, too, by Sir John—is that in learning, one is dealing with more radical kinds of new associations, that is, big new associations that would be more wide-reaching in neuronal terms, for example, the conditioning of a given response to some new signal, and the like. Those phenomena that we were discussing earlier, on the other hand, are essentially a reinforcement of what is already there, that is, of the already existing networks. You could argue that this is not enough for learning, that learning requires new connections on a much broader scale, and particularly--yes, don't hesitate to interrupt, because I'm going to interrupt myself and change all this story anyway. (Laughter)

MILLER: I don't think it is essential to have completely new associations.

SPERRY: Right, that is exactly the point I'm coming to. I said initially that these phenomena might well be exactly what we're looking for, but I am now pointing out certain objections. My next point is that there are objections to override these objections.

KRECH: You don't really believe the law of effect, either, I trust.

SPERRY: I think I do believe the law of effect, as I understand it, at least at certain levels of discourse and in certain situations. I appreciate the controversy about whether it really operates or not, but I think what I'm going to say may resolve this point as not being critical for the present thesis.

McGAUGH: I can't resist making one comment regarding the law of effect. You said that if memories are not reinforced, they are forgotten. I think the evidence is pretty clear that if animals are not reinforced they stop doing things, but whether or not they remember how to do them is another question entirely.

SPERRY: You can refer this to motor learning?

McGAUGH: I'm referring to all kinds of learning. I have some data I will present later on.

SPERRY: O.K. It sounds as though it may all be partly a matter of terminology. Anyway, to continue with additional objections, we have the phenomena of generalization, and sensory and motor equivalence effects, which also have seemed to some theorists to point against specific network changes that one can pin down, and to point instead in the direction of more plastic engrams in the form of dynamic schemata, and so forth.

Well, as I have been forced to admit already, I don't feel myself that we can really exclude, on the grounds of these objections or others, the possibility that phenomena of the kinds discussed earlier constitute the organic basis of memory. The interplay between the dynamics of the brain excitation and the structural engram is suffi-

ciently complicated, and has enough possibilities, to take care of all such objections. One can, in fact, make a very good case for the possibility that learning really is just a reinforcement of neuronal associations already there. In this same connection, remember that the first response, the first experience, the first conditioned reflex, is always made without the memory of previous similar experiences and responses, so the original machinery is already capable of the first reaction.

FREMONT-SMITH: May I just mention George Coghill. It was his conviction that every experience led to specific organic growth of the nervous system. I don't know that he had any evidence for it, perhaps, except in the embryo, but this was his belief for the total organism.

SPERRY: I think, yesterday, Sir John came out rather strongly with the impression that, physiologically, synaptic changes are really the most likely place to look for memory. This, of course, has been the orthodox point of view throughout the whole history of memory trace and engram theory. The synaptic junction has always been suspect number one. Even so, I think we do have to consider the possibility that the changes could be of another type. The engram changes might, instead, affect the endogenous physiologic properties of the neurons that I referred to earlier, rather than their contacts with other neurons; I am thinking here of changes that would affect the internal machinery of the neuron for, say, its detection and/or discharge of particular pulse patterns, for example.

ECCLES: I agree with that. If I may interrupt, as usual, I did mention this point—my point No. 3 was, in fact, the great complexity of dendritic structure, which is much more complex a receiving machine than we had hitherto imagined, with a possible local response with synapses here and there all over the great branching dendritic apparatus of the pyramidal cells. It may be the effectiveness with which this activity moves down through the pyramidal cell which is important. Is that related to your point?

SPERRY: Yes. That would be the detector aspect, but, also, the internal or motor machinery of the cell, to give it an intrinsic tendency to discharge in a certain way, that is, as a burst, or as a train, regular or irregular, new internal clock effects and that sort of thing.

ECCLES: Yes, that is mostly dependent on feedback, I think.

SPERRY: Well, it could be, I suppose. I'm blithely ignorant about a great deal of the endogenous physiology and biochemistry of neurons so I can speculate more freely on these things.

MILLER: I would like to point out that while changes in the characteristics of the neuron are an entirely possible basis for learning, there are certainly many more possibilities for memory

if the changes are in the synapse, because there are many more synapses than there are cells.

KRUGER: If one changes the input to a given cell, its characteristics would inevitably change; in other words, one can change the input to a cell without modifying its internal structure and its characteristics of output.

TEUBER: In this context, I said earlier that perhaps we're looking at the wrong place when we look at the synapse, not because I have any basis for thinking that it is, in fact, the wrong place, but simply because I wanted to make the same point Dr. Sperry just made, that we should keep some of the alternatives in mind.

One alternative was, perhaps, a very simple-minded one: If, without a change in the synaptic apparatus as such, axons or, possibly, dendrites could somehow modify their propagation velocities, maybe actually by changing their diameter during certain functional states, we would have all the mechanisms we want, without altering synaptic linkages per se. Just by changing the time bias of arriving impulses in the convergent pools, we would have, again, a basis for fluctuating change, or even enduring change. This is just one of the many several possibilities to keep in mind; it was first suggested, I believe, by Donald MacKay. *

PRIBRAM: And let us remember that Dr. Kruger showed beautiful evidence that fiber-size diameter does change. If nothing else, if all the other things were, perhaps, a little shaky, that was the one finding that was very clear-cut.

KRUGER: At least, remyelination can occur.

PRIBRAM: Yes, and the chances are that this has something to do with fiber-size diameter, if fibers are involved at all.

KRUGER: The size of the axon, however, does not bear a simple relation to axis cylinder size.

ROBERTS: Could we invoke some chemistry, too, and say that configurations, or the changes in the configurations on these conducting surfaces, might be very important. If the degree of hydration or hydrogen bonding of certain structures could be changed, which alcohol or urea or similar substances might do, then the properties of the surfaces would be changed. Is that an admissible possibility in this instance?

SPERRY: Yes.

PRIBRAM: In this context, we ought to mention Frank Morrell's experiments (29) in which he showed, though perhaps not conclusively, that changes do take place in the firing patterns of neurons when they have been submitted to fields of DC potentials. He has not, of course, isolated a single neuron, so the change he finds may reflect a change

*Personal communication.

in the total net or a small part of the net he is examining.

KRUGER: However, such changes really could affect virtually anything. They could affect the ribosomal content of an adjacent glial cell; they might affect the entire metabolism of anything nearby. In essence, they could even, presumably, be operating on the capillary network in some way, in which case it would be reflected in the capacity of a nerve cell to discharge impulses to a constant input condition, assuming that this could be maintained, with an electrode pushing upon a cell for a considerable length of time. This would be an extremely difficult experiment to evaluate, one way or the other.

MILLER: But, Dr. Pribram, aren't these changes to a specific rate of discharge that Dr. Morrell has just imposed on these neurons? For example, he will stimulate the network with 10/sec in one experiment, under the influence of this persisting DC potential, and then the 10/sec discharge will continue after he stops stimulating. In another case, he will stimulate at 5/sec while subjected to the continuous DC, and then the 5/sec discharge will persist. So I don't think it could be just a simple effect of the DC on the capillaries, giving the cells more oxygen or less oxygen, because it is also determined by the rate of impulses that are put in. It does look a little more like learning, therefore, although it may not be learning, than just simply changing the rate of firing by changing temperature or something as crude as that (29).

GRENELL: We might mention, too, that, from the structural point of view, the surfaces of all these neurons are constantly changing under continuing circumstances of activity. It seems to me at least a reasonable possibility that changes in dimensions can go on in this system, in relation to some of the glial pulsations which have often been reported. The glia may "stick their heads up" from this point of view as well as from any others, because, if they are pulsating—and they have been shown to be contracting under various circumstances—this should change the system to some degree, too.

RIOCH: I get an impression that it is no longer a problem of how to get memory and variations and so forth, but it is getting to be a very severe problem to know how one gets home after a party. (Laughter)

SPERRY: This dominant-focus phenomenon which is relevant here, and certainly one of the interesting new leads, might involve changes in the intrinsic properties of the neuron. Endogenous properties of the neuron and ways of developing, sustaining, and altering them is a neglected subject that will probably receive a good deal more attention in the future. Into the collection of possible internal changes that have been mentioned, one could add changes in the neurofibrils affecting conductance through electronic or other effects. Dendro-dendritic relationships may be mentioned here, along with

dendritic growth; also "gliapse" and purely glial changes cannot be excluded.

In short, I would think it best to admit at this stage that we are very much in the dark with respect to the physiologic and anatomic basis of the engram or permanent memory trace. And we are not much better off with regard to the biological basis of short-term memory.

Again, I am not particularly satisfied that it is just a continuing reverberating excitation that carries the short-term memory.

PRIBRAM: Here, may I ask if anybody in the room knows of any evidence for any kind of reverberating or temporary mechanism of this sort?

McGAUGH: Are you referring to Burns' (10) isolated cortical-slab preparations?

PRIBRAM: That is not a reverberatory mechanism; that is spontaneous activity. There is a difference.

McGAUGH: It is induced, isn't it?

PRIBRAM: Changes in it can be induced.

GRENELL: I don't think there has been any evidence for that, Dr. Pribram. I would, at this point, be strongly in favor of F. O. Schmidt's statement to the effect that the use of the term, "reverberating circuit," is just cloaking another process; that, if there is such a process, it has to be looked at in molecular terms, because there is no other way of explaining this sort of thing without some kind of macromolecular change in cells that is really the basis of it. For short-term memory, a reverberating circuit is not really needed; all that is needed is a network firing.

PRIBRAM: Good! That's the statement I wanted.

UTTLEY: I'm not clear about that; I mean, if we accept the idea of columns in the cortex, and various people are discovering that there are isolated columns, I should have thought such a column of cells, if there is a fairly isolating wall around it, would be able to store reverberatory patterns.

GRENELL: Well, that may be, but there certainly is no actual evidence to support it; in fact, there is a very great deal of direct evidence in the other direction.

JOHN: I'm not sure what you're asking, Dr. Pribram. Are you asking for evidence that reverberation exists, or that it plays a role in the consolidation phase?

PRIBRAM: No, that it exists at all.

JOHN: What about the circulating patterns that Verzeano and Negishi reported (47)?

ECCLES: That's the thing I wanted to say. Creutzfeldt and Jung (13) have confirmed Verzeano (48) in showing the existence of circulating patterns of impulses.

I believe, therefore, the thalamocortical reverberatory circuit notion has very little in the way of solid evidence to support it.

ECCLES: I think it is relevant here to describe the rhythmic thalamic discharges which Adrian (1) discovered in 1941, and which Chang (12), in 1950, attributed to reverberatory circuits between the thalamus and the cortex and not just to discharges from the thalamus. In 1950, Adrian repeated his old experiments and showed that the cortex was not essential for the rhythmic thalamic discharge. We have re-investigated this thalamic discharge quite recently and have proposed a mechanism whereby the thalamus will generate a rhythmic discharge without a reverberatory circuit (3). Essentially, our hypothesis builds upon the large inhibitory postsynaptic potentials of thalamic neurons and the rebound from this inhibition. The pathway requires only negative feedback from thalamic cells via axon collaterals to the inhibitory cells, and so back to the thalamic cells, generating there the large and long (100 to 200 msec) inhibitory postsynaptic potentials. It is entirely within the thalamus and has a cycle time of 100 to 200 msec set up by the duration of the inhibitory potentials.

KRUGER: Wasn't Adrian's argument that he could record this repetitive discharge from the exposed white matter?

ECCLES: Yes, and he anesthetized the cortex and got just the same thing.

PRIBRAM: Malis and I also removed the cortex and repetitive discharge could still be recorded. *

SPERRY: I think the next point I was about to lead into was this: that not only is it quite possible that we may already have the answer to the memory trace, but, perhaps more important, we probably would not recognize the answer today if we did have it--even if it were served to us on a silver platter fully outlined, physiologically, and complete with a sheet of instructions for molecular analysis. The reason is that there are so many unknowns between the neural engram at the one level, and memory, as we know it, at the behavioral level. These unknowns lie partly at the level of neuronal physiology and synaptology, but mainly at the level of cerebral integrative physiology, that is, in the problems of the patterning and spatio-temporal organization of brain excitation.

Before an answer at the molecular or cellular level is going to mean much, we are going to have to work through a lot of these other intermediate unknowns. The problem of the anatomy of memory right now is not so much to find the answer but to find the problem. To formulate the problem of the engram clearly, we have to work our way down to it. In a sense, we are looking for the secret code of an unknown code of subjective meaning and information which, in itself,

*Malis, L. and K. Pribram: Unpublished data.

is pretty insubstantial stuff. We have our images, our memories, our impressions of last year's vacation or what not, or we see new movement skills or new responses, but those, of course, don't translate very easily into engrams. For this latter, we have to know something about the intermediate patterns of brain excitation that underlie such behavioral phenomena.

To code the subjective or even motor phenomena to be remembered into the corresponding spatio-temporal patterns of cerebral excitation is at present utterly impossible, even in principle. It requires, at least in part, a solution to the mind-brain problem, an impossible step in itself at this stage. But after we've cracked this first coding problem we then have to go further. We have to code these spatio-temporal patterns of brain excitation into the spatial or frozen patterns of the static structural engrams. Here, we've got another coding problem to handle and, at this stage, we are working at two or three removes from a starting base that, in the case of most memory, that is, subjective memory, is already a rather intangible will o' the wisp. You can see how easy a general state of confusion surrounding the whole could result.

PRIBRAM: Oh, it's not as bad as all that, really, Dr. Sperry.

SPERRY: But I'm afraid it really is; can you see any one feature of the problem specifically that is less troublesome than I've indicated?

JOHN: I'm not at all sure that one has to code these things as "frozen patterns" of engram.

SPERRY: The permanent memory trace almost has to be spatialized and, therefore, to be a system quite different from the dynamic, temporally organized cerebral excitations that produce it and which it reactivates.

PRIBRAM: I think Dr. Von Foerster will point out that he doesn't think it is impossible to get from mind to brain. I think there are some logically tight things that can be said about these relationships.

VON FOERSTER: We can do it, with the help of computers. I don't think it's as bad as all that.

SPERRY: When the chemist talks about the memories of a lifetime and the feasibility of coding them into RNA, this whole "problem within problems," as I've just outlined it, is exactly what he is up against. The more cautious physiologist may work with the conditioned reflex or with motor memory, and perhaps avoid the subjective phase of the problem. O. K., but even so he's still obliged to search for the unknown code of an unanalyzed unknown, the underlying cerebral excitation.

KRECH: May I add a slightly pessimistic note—one which gives a very, very foreshortened and very biased account of the history of

surface connections and their strength. The increase in likeness would be proportional to the amount of material exchanged, which in turn, within limits, would be a function of strength and frequency of stimulation. It is even possible to suggest that as a result of activity at the synapse there is an increased relatedness between the glial cells and the connective tissue and endothelial cells in their vicinity. In the case of exchange between less differentiated units with highly specified units, such as are found in primary sensory or motor tracts, the differentiating influence ordinarily would operate largely in the direction of the less differentiated unit, whether pre- or postsynaptic, the less differentiated neuronal elements becoming more like the more highly differentiated ones.

SPERRY: I believe we have skipped over a point that is relevant here, namely: Not only would we not recognize the answer today if we saw it, but, further, even if it were recognized and demonstrated without question that the memory trace in physiologic terms is such and such change at the synapse, occurring under such and so conditions, this answer, outlined at the physiologic level, probably would not help much in explaining many of the more puzzling and more interesting features of memory that intrigue us as we commonly face the problem at the behavioral level.

For example, had we the answer now to the synaptic change, it probably would not tell us how, specifically, the engram for one memory differs from that for another. It would not tell us how different kinds of memories are classified and filed with reference to one another.

Such an answer wouldn't help us understand how the subjective meanings are encoded, first into brain excitation and then into engram patterns, and probably wouldn't even give us the general coding principles involved. It wouldn't tell us why the time arrow in reactivation of engrams always seems to work in the right direction. Once we've got temporal patterns, like a new melody, spatialized into a permanent trace system, there is no apparent reason now why the associations should not work backwards as well as forwards, yet they do not. It wouldn't tell us how we can retrieve the proper memory instantly from out of those thousands of others that are available.

ECCLES: May I make a comment about the direction? I think I could envisage, in imagination, or even draw a model of a synaptic hookup of a system of neurons, which could work only one way. It wouldn't work in the reverse.

SPERRY: Yes. Now you're thinking more in terms of a pattern of synaptic changes or a model much larger than the individual synaptic change that you were talking about earlier. You're beginning to get into the rather different problems of the patterning and distribution of the synaptic changes, which is my point.

ECCLES: Of course. I would agree, naturally, that there are millions of neurons in the simplest engram, organized, with pathways or, shall we say, effectiveness of synapses, giving this particular pattern.

SPERRY: Yes. I'm coming to that. To continue, insight into the nature of the synaptic change would not explain either why traces don't get all mixed up with each other, or why some experiences tend to produce lasting, long, powerful memories, while others are evanescent, and many other questions about memory at the behavioral level, for the reasons I've indicated.

Now some of you may have noticed that I was careful to say at the start that discovery of the nature of the engram at this point probably wouldn't help to explain many of the interesting features of memory. Some of the new molecular theories of memory that have popped up in recent years do encode, or, at least, purport to encode experience into a molecular form, by the shuffling of RNA bases and this sort of thing. In other words, the nature of the engram hypothesis in molecular terms is such that some of these behavioral and organizational aspects of the memory problem are approached, in principle at least, within the molecular model. The molecular theories, that is, tend to incorporate the answers to coding and patterning problems.

A critical point in regard to this whole problem is raised by the simple question of what it is in any given theory that distinguishes the neural engrams of one memory from those for another. If this distinction between one engram and another is a matter of molecular structure, then many of the interesting features of memory, in contrast to my earlier statements, would come out in the molecular analysis. This means a coding of experience, memory, meaning, at the molecular level.

But, on the other hand, if the distinction between memories comes down to a matter of the distribution within the brain networks of essentially the same kind of molecular change, then the foregoing statements continue to apply.

Any synaptic change or change in endogenous neuronal properties will, of course, have a chemical basis that very likely may involve RNA changes, among others. But, in this case, we'd not think of the chemical analysis as a molecular explanation of memory, in at all the same sense as where macromolecular coding is involved. The coding in this present alternative resolves into patterns of distribution of changes within the brain networks. This, in a sense, is coding at the nerve network level, not at the molecular level.

Now we come to the next point I want to emphasize, namely, that the phenomena that were discussed earlier, such as synaptic growth and potentiation by use, fall within this latter "network" cate-

gory, that is, it is the patterns of synaptic changes through the brain that distinguish different engrams; it is the patterns of the changes in connections that count. To discover the physiology or chemistry of the synaptic change will still leave all the patterning and coding problems unsolved. This is in line with what has been the orthodox approach to the engram problem for years. It is largely the postwar developments in our knowledge of RNA and DNA, and so on, that has prompted these other theories that hope to encode memory at the much lower, molecular level. I think the distinction between these two approaches to the anatomy of memory is important.

Any molecular coding has to be expressed, eventually, through the language of neuronal physiology. I've already indicated the extent of our ignorance on this score, and the many different possible factors at the neuron and network level that could be critical. Until we can say more precisely what kind of physiological or anatomical change is involved, there are few constraints to the speculation boom regarding possible molecular mechanisms. We very much need answers at the physiological level to orient theorizing at the molecular level, and to get the answer at the neuronal or synaptic level requires, in turn, many answers to be worked out at the integrational level.

I outlined my own preference, or bias, in this general bimodal spectrum of approaches to the memory problem some 10 years ago (42) in what, I guess, you could call a preparatory set type of theory. It, too, falls more within the network than the molecular category, and rather far out away from the molecular side toward the other extreme.

In this notion, the mnemonic information is not coded directly into memory traces at all, or at least a large part of the mnemonic information is not coded into engram form, but is carried by the contextual dynamics of the selective patterns of background excitation that are always needed to activate any particular engram. That is, the engram of the memory trace and the excitatory context in which it is aroused—these two factors are cofunctions and are mutually interdependent. The coding then comes out in terms of the combination. It is a higher level kind of coding, not coding at a molecular level. Much of the information doesn't have to be put into the static trace system; it comes out by reactivation in the combination of transient excitatory phenomena plus the engram effects.

You can see, then, that the encoding of information and memories, as we think of these at the behavioral level, becomes an extremely complicated business, and also why it is that discovering the physiologic or chemical nature of the trace will not, on these terms certainly, give us the whole answer.

Long ago, I spent most of a year trying to work out a theory of memory without traces, that is, without engrams or any lasting tissue changes. I think the idea that attracted me had features in common

with, but was a little different from the one that Dr. Von Foerster prescribes. It was not the continuing reverberation concept, either. My colleagues called it a "perturbation" theory of memory, the term being used as it is in astronomy; the idea is that any rolling, moving, dynamically organized and perpetually active system, once it has been perturbed or changed, will never move the same thereafter, and if one organizes the controls, feedbacks, retainers, and all, in the right way, one can carry things along by dynamic organization without having to keep all the details going in local eddies or in structural changes in the tissues.

You will see that the notion falls down, of course, in that it depends on a continuing organization in the dynamics. The survival of memories through deep anesthesia, concussion, electroshock, and the like, would seem to rule it out. But, nevertheless, it is instructive to go through an exercise like this to appreciate how much of behavioral memory one can handle, conceivably at least, without resorting to permanent traces, how much of the meaning and so on can be handled by the contextual dynamics.

Every once in awhile I am prompted, as by this Conference, to go back and concentrate on the memory problem, to look at the synapse and the neuron and even the glia in search of the memory trace. Then, as I begin to think about it, all these complexities in the memory problem, as I've outlined them, start to come back and get reactivated. At about this point I again decide that maybe, after all, the very questions of cerebral organization that our lab is currently working at are not so far removed, and may be as direct an approach as any to the central coding problems involved.

RIOCH: Dr. Sperry, you are saying, among other things, that the continuing input during the interaction of the organism with the environment is playing a very considerable role?

SPERRY: Yes, but I'd include the association generated internally as well as externally. I illustrated the notion with reference to the "simple" memory involved in the conditioned reflex, contrasting it with the traditional idea that a conditioning stimulus acquires new temporary connections to some motor output, and the problem is to find the new fiber pathways worn between them. I pointed out that there probably are no such pathway changes to be found at all, that this new functional linkage is taken care of by the contextual dynamics, that is, a preparatory set that guides the conditioning stimulus into the new channels and discharges it properly. The engrams are conceived to reinforce this preparatory set or expectancy, and this means an entirely different kind of engram or engram pattern than the wearing of traces from the sensory to the motor center.

RIOCH: I subscribe to this very strongly because, in psychotic patients and in normal subjects under extreme stress, we get fantas-

or active movement is one that is initiated not by one, but at least two sets of impulses—one going out to the musculature, the other, centrally, to the sensory systems. It is this associated central discharge —the "corollary discharge," which prepares the sensory systems for the corresponding reafferent input, that is, the input resulting from executing the intended motion. The "corollary discharge" is, thus, a central set or state of readiness, a schemata, as Dr. Sperry pointed out just a few moments ago. In fact, Dr. Sperry wrote about these matters a good 14 years ago (41) as did Von Holst (24).

These hypotheses about central states built up as residues of active movement are so attractive because they might give us a handle for the extremely difficult problems of recall. One may think of the amnestic syndromes that Dr. Rioch mentioned. In many of these states, one does not get the impression that traces (whether neuronal or molecular) are destroyed en masse. Quite to the contrary, one cannot help but think that the problems of these patients revolve around an inability to retrieve the traces that are there; there seems to be an almost complete inaccessibility of the memories they have stored.

JOHN: Perhaps an example of the other side of the coin, the facilitating contextual action, can be provided from the work of Grastyán (21) and of Wyrwicka (50).

Animals were either conditioned to central stimulation, or else conditioned and then centrally stimulated. These workers report that if the animal is in the training situation, and so oriented as not to see the manipulanda when stimulation occurs, quite frequently the animal will simply sit. However, if the manipulanda are within the visual field of the animal, stimulation will reliably elicit performance of that response.

MILLER: I don't want to disagree with anything that has been said or to discount any of these complexities, but I would like to say that it is conceivable, on the other hand, that something can be discovered at a simple level, the level at which Sir John has been working. If something simple is discovered, it is also conceivable that it will be enormously valuable. It certainly won't solve all our problems, but it might be an enormous step forward.

SPERRY: I would hate to have given any other impression.

MILLER: I want to encourage the continuation at the molecular level.

PRIBRAM: We must solve these problems at all levels, probably simultaneously, and show the necessary connection between the solutions at each level.

MILLER: Yes. We can't tell where the breakthrough is going to come, but a breakthrough may yield such enormous progress that we can scarcely imagine how valuable that progress will be.

tic confirmation of this kind of thing; that is, the complete losses of memory, but complete recovery under a changed situation.

I don't see any way of explaining it except in terms of always looking at the organism as interacting with the environment. I think one of the difficulties we have is with our language. A lot of these terms such as "memory" are static, and we haven't yet learned to think in ongoing interactional terms.

SPERRY: I seem to be left now with a general feeling that I may have given the impression that I discount the molecular approach too much. This is not the case. Neither the molecular nor the network approach can be excluded at the present state of our knowledge. They are alternatives, neither of which should be overlooked.

RIOCH: There is another aspect to the molecular approach which concerns the assumption that different engrams are developed for processing different input. This is not necessarily so at all parts of the processing system. Certain subdivisions of the process may be identical for different inputs.

SPERRY: I think there is another point I ought to mention. I have posed two more or less distinct alternatives, a kind of dichotomy. Now, when one pushes into these matters further, one finds that there are intermediate possibilities that, for the sake of clarity and lack of time, I omitted.

LEVINE: Your ideas are extremely appealing. The greater bulk of our work deals with the effects of certain events in infancy upon later behavior, and the whole psychophysiologic process. If we had to deal in terms of specific memory traces, we would be forced to face the fact that a rather minimal amount of stimulation sets up an enormous number of memory traces. In the context of Dr. Sperry's remarks, the effect may be simply the reorganization of some form of central nervous system function, affecting a wide variety of behaviors, from the animal's response to stress to its ability to discriminate patterns, etc. It just didn't seem that there could be this many subjects or independent traces set up. Rather, some form of overall dynamic reorganization of the nervous system seems more likely.

SPERRY: It is much like the "schemata" approach.

PRIBRAM: Right; Bartlett's type of thing (8).

TEUBER: The reason I brought up the experiments of Held and Hein (23) earlier was because I think we are dealing with a very peculiar kind of perceptual learning: the early perceptual learning in the acquisition of sensory-motor coordinations by very young animals. They were trying to show that "voluntary" or self-initiated motor patterns might be a sine qua non of the laying down of early memories and other recall later on.

This view of the relationship between movement and perception has intriguing consequences. It involves the idea that a "voluntary"